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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/996,008	11/28/2001	Kazuya Mitsuhashi	14879-093001 / D1-A0011Y1	2666
26161	7590	04/06/2004	EXAMINER	
FISH & RICHARDSON PC 225 FRANKLIN ST BOSTON, MA 02110			PAK, YONG D	
			ART UNIT	PAPER NUMBER
			1652	

DATE MAILED: 04/06/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/996,008

Applicant(s)

MITSUHASHI ET AL.

Examiner

Yong D Pak

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 January 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-7 and 20-46 is/are pending in the application.
- 4a) Of the above claim(s) 20-29 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7 and 30-46 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

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DETAILED ACTION

The amendment filed on January 26, 2004, amending claims 1-7, canceling claims 8-19, and adding claims 30-46, has been entered.

Claims 1-7 and 20-46 are pending.

Election/Restrictions

Claims 20-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 16.

Notice of Possible Rejoinder: The Examiner notes that if claims 1-7 and 30-46 are found directed to an allowable product, then claims 20-29, which are directed to the process of making or using the patentable product, respectively, previously withdrawn from consideration as a result of a restriction requirement, would now be rejoined pursuant to the procedures set forth in the Official Gazette notice dated March 26, 1996 (1184 O.G. 86; see also MPEP 821.04, *In re Ochiai*, and *In re Brouwer*).

Response to Arguments

The rejections of claim 8 under 112, 1st paragraph has been withdrawn in light of the cancellation of claim 8.

Applicant's arguments filed on January 26, 2004 of the rejection under 103(a) have been fully considered but they are not persuasive.

Claims 1-8 and the newly submitted claims 30-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Galkin et al. in view of Slusarczyk et al. and Tishkov et al.

Applicants argue that one of ordinary skill in the art would have read Tiskov et al. as teaching away from making a substitution at Cys-256 for potentially decreasing the thermostability of the enzyme (Remarks, page 11). The examiner disagrees.

The motivation of making a substitution at Cys-256 or at other cysteine residues is to ameliorate thiol-coupled inactivation of the enzyme. It is known that that nearly all NAD-dependent formate dehydrogenases are inhibited or inactivated by reagents that modify sulfhydryl groups (Slusarczyk et al.). While the resulting mutants may be less thermostable than the wildtype enzyme, the reaction can be kept below the inactivation temperature. Further, the claims are drawn to formate dehydrogenase that have greater activity and not to enzymes having greater activity and greater thermostability.

Applicants also argue that the references do not teach any advantage of using a *Mycobacterium vaccae* formate dehydrogenase or that the mutant enzyme has increased activity in the presence of organic solvent (Remarks, page 11). The examiner disagrees.

One of ordinary skill in the art would have been motivated to use a *M. vaccae* formate dehydrogenase because its specific activity is comparable to other formate dehydrogenases and the enzyme is used in biotransformation of chemical compounds.

The reaction medium of the reaction utilizing the enzyme is carried out in organic solvents. Also, the fact that appellant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious.

Applicants also argue that the combined references do not teach or suggest modification of Cys-146 since Slusarczyk et al. do not teach modification of a cysteine residue corresponding to Cys-146 of the instant invention and since some mutants have lower activity compared to the wildtype. The examiner disagrees.

Since there is suggestion and expectation that modification of a cysteine residue will increase the enzyme's activity, there is sufficient motivation of making modifying the cysteine residues of SEQ ID NO:2. It is not uncommon nor an undue burden to modify seven residues in an enzyme and site-directed mutagenesis is very routine in the art, as well as generating mutants having double/triple mutations. Although modification of some cysteine residue may not increase the enzyme's activity, one of ordinary skill in the art would have been motivated to make them. Further, Slusarczyk et al. teach that Cys-23 of is exposed to the surface of the enzyme and Cys-262 is buried in the protein and therefore, one of ordinary skill in the art would recognize that modification of Cys-262 might lead to disruption of the protein structure thereby decreasing its activity. Therefore, it is not unexpected that some mutants will have a decreased activity compared to the wildtype enzyme.

Applicants also argue that there is no suggestion for making multiple mutations. The examiner disagrees.

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It is not uncommon nor an undue burden to generate mutants having double/triple mutations.

Applicants also argue that there is no motivation to modify Cys-6 since the residue is likely essential for enzyme activity. The examiner disagrees. This residue can be substituted with a serine residue because serine is a structural analogs of cysteine and the change gives information about the role of the sulfur atom in cysteine residues in formate dehydrogenase stability.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

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consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 30-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Galkin et al. in view of Slusarczyk et al. and Tishkov et al.

Galkin et al. (form PTO-1449) teach a formate dehydrogenase from *Mycobacterium vaccae* that is 100% identical to the formate dehydrogenase of SEQ ID NO:2 of the instant invention (Table 1, page 482). Galkin et al. teach that the formate dehydrogenase of *M. vaccae* is 99% identical to that of the dehydrogenase from *Pseudomonas sp.* (page 482). The two enzymes are physicochemically very similar to each other (abstract). The formate dehydrogenase from *M. vaccae* has only seven cysteine residues (figure 1).

Galkin et al. also teach that replacement of Cys-255 of the *Pseudomonas sp* resulted in a mutant enzyme that was stable to air oxidation (page 1995). This cysteine residue corresponds to the cysteine residue at position 256 of SEQ ID NO:2 of the instant invention.

The difference between the reference of Galkin et al. and the instant invention is that the reference does not teach a mutant dehydrogenase having substitutions at position 6 and 146 of SEQ ID NO:2.

Slusarczyk et al. (form PTO-1449 - FEBS 2000) teach that nearly all NAD-dependent formate dehydrogenases are inhibited or inactivated by reagents that modify sulfhydryl groups or catalyze oxidation of SH-groups by molecular oxygen. Slusarczyk

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et al. mutagenized all the cysteine residues in the primary structure to increase the enzyme's stability by alleviating any thiol-coupled inactivation (abstract). Slusarczyk et al. also teach that the cysteine residues were substituted by aliphatic amino acids such as alanine and valine (page 1286).

Similarly, Tishkov et al. (form PTO-1449) also teach mutant formate dehydrogenases wherein a cysteine residue is substituted in order to increase the enzyme's stability. Tishkov et al. teach that Cys-255, which corresponds to Cys-256 of the instant invention, was substituted with a serine residue because serine is a structural analogs of cysteine and the change gives information about the role of the sulfur atom in cysteine residues in formate dehydrogenase stability (page 976). Tishkov et al. also teach that Cys-5, which corresponds to Cys-6 of the instant invention, is involved in the stability of the enzyme (page 979).

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to mutagenize cysteine residues of the formate dehydrogenase of Galkin et al. following the teachings of Slusarczyk et al. The motivation of substituting cysteine residues with serine, alanine or valine residues is to alleviate any thiol-coupled inactivation of the enzyme, there by increasing its stability. One of ordinary skill in the art would have had a reasonable expectation of success since site directed mutagenesis is performed routinely in the art and Slusarczyk et al. successfully showed that mutagenizing cysteine residues increase the stability of the enzyme. Also, systematically substituting seven cysteine residues with serine, valine or alanine is ordinary in the art and mutations of this nature are routine in the art.

No claim is allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak
Patent Examiner



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